Original Communications

HERITABLE DISORDERS OF CONNECTIVE TISSUE

IV. The Ehlers-Danlos Syndrome

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HISTORICAL NOTE

NONE of the hereditary disorders of connective tissue, except possibly osteogenesis imperfecta, has as ancient a history as does the Ehlers-Danlos syndrome. The first definitive case* of this syndrome seems to have been described in 1682[94] by Job van Meekeren, a surgeon of Amsterdam. In Fig. 1 is presented van Meekeren's illustration of the "extraordinary dilatability of the skin" in a 23-year-old Spaniard who could pull the right pectoral skin to the left ear, the skin under the chin up over the head like a beard, and the skin of the knee area out about one-half yard. On being released, the skin retracted promptly to fit snugly over the underlying structures. This phenomenon was limited to the skin of the right side of the body.

Various dermatologists, including Kopp[44] and Williams[102] published scattered references to this condition, which was usually observed as a curiosity in "India rubber men" of side shows. Kopp's report in 1888 is particularly noteworthy since he described the condition in father and son. Gould and Pyle[33] published the photograph made in Budapest in 1888 of an exhibitionist named Felix Wehrle, "who besides having the power to stretch his skin could readily bend his fingers backward and forward." Du Mesnil[23] in 1890, Williams[102] in 1892, working in Unna's laboratory in Hamburg, and Unna[93] himself in 1894 reported on histologic studies. In general, these authors were puzzled by the absence of more specific changes and found difficulties in the interpretation of what they did

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*I have been unable to find documentation for the statement[10,70] that Hippocrates[51] described the Scythians as having skin and joint changes of the precise type seen in this syndrome.

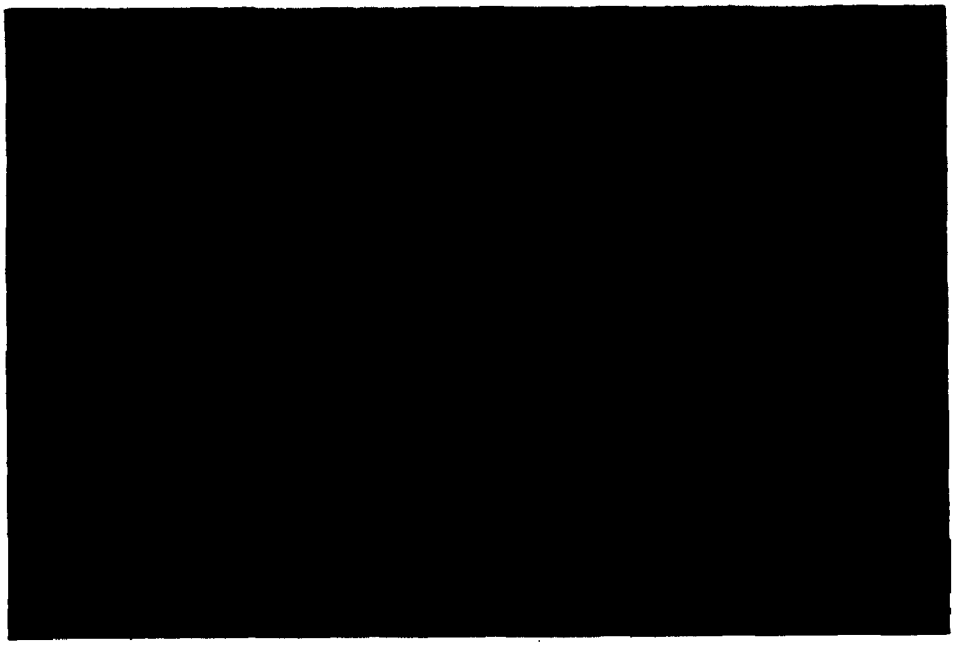
find. The contribution in 1901 by Ehlers[25] of Denmark consisted of pointing out the associated loose-jointedness and the subcutaneous hemorrhages which are prone to occur. Danlos[15] in 1908 rounded out the clinical description with inclusion of the tumors which may develop at subcutaneous sites.

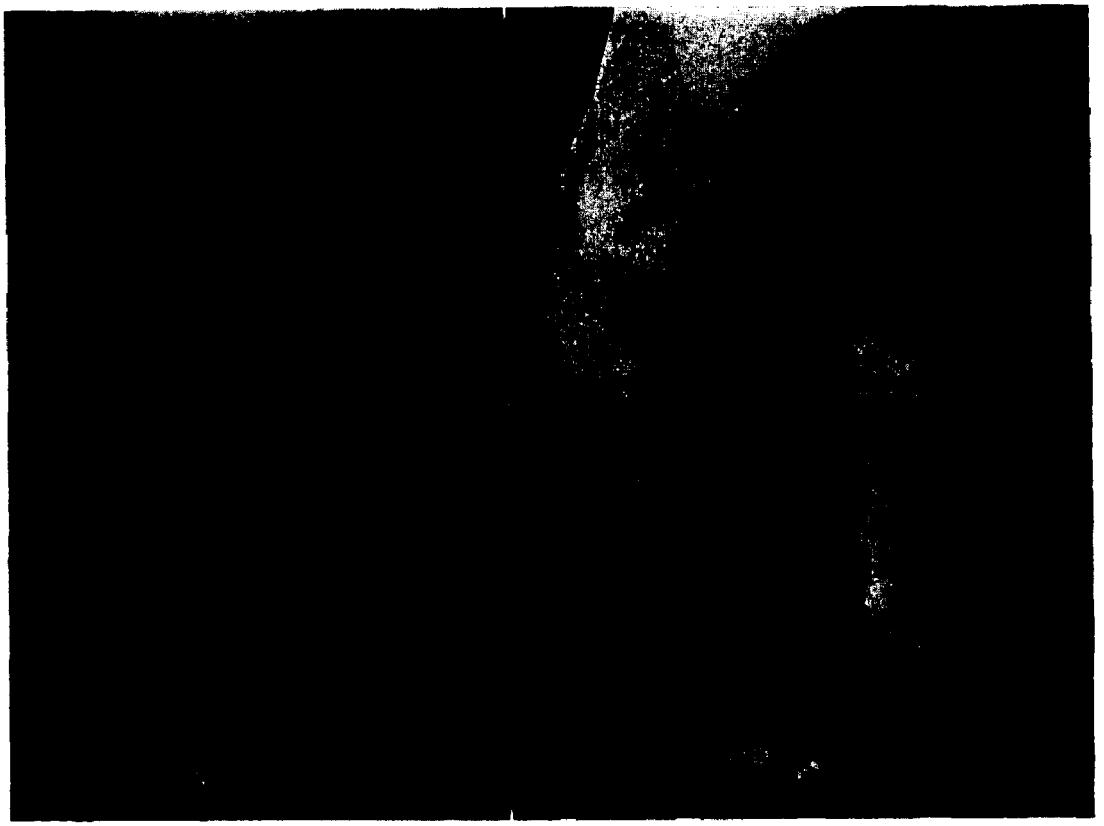
Fig. 1.—Job van Meekeren's case of "extraordinary dilatability of the skin."

"In the year 1657, in the presence of the very distinguished John van Horne and Francis Sylvius, professors of medicine in the famous academy of Leyden, as well as of William Piso and Francis vander Schagen, practitioners of Amsterdam, we saw in our hospital a certain young Spaniard, 23 years of age, by the name of George Albes, who with his left hand grasped the skin over his humerus and right breast and stretched it till it was quite close to his mouth. With each hand he first pulled the skin of his chin downward like a beard to his chest, hence he lifted it upwards to the vertex of his head so as to cover each eye with it. As soon as he removed his hand the skin contracted to reassume its proper smoothness. In the same way he pulled the skin of his right knee upwards or downwards, to the length of half an ell; then it easily returned to its natural position. It was worthwhile noting that the skin which covered the forementioned parts on the left side could not be extended since it firmly adhered to them. It has, thus far, not been possible to learn the cause [of this anomaly?]."—Translated from original Latin by Dr. Owsei Temkin.

Many terms have been used for this syndrome or more often for its individual features. As in the case of the Marfan syndrome, the eponymic designation seems preferable, since it does not convey any connotations of the invariable occurrence of an individual manifestation or any ill-founded notion of the nature of the basic defect. "E-D" is the abbreviated label which will be used frequently in this presentation.

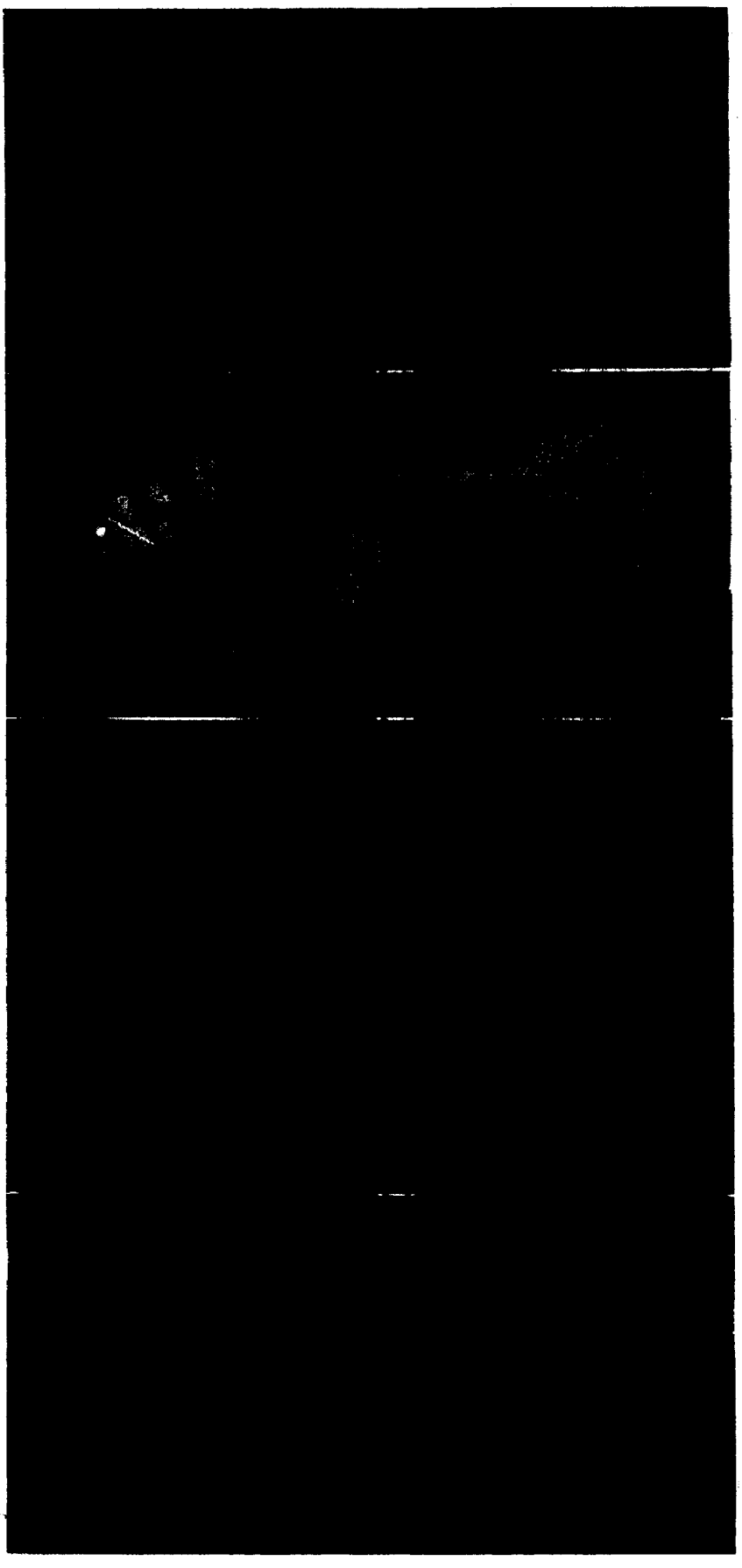
This survey of E-D is based on a personal study of eight kinships, each with at least one affected person. Comparison of the findings with those reported in the literature is made.





B. *C.*

Fig. 2.—Changes in skin and joints of 16-year-old girl, D.V. (A 41965). *A*, Cutaneous hyperelasticity. *B*, Normal position of knees. Note papyraceous scars over the knees and flat feet. *C*, Genu recurvatum, more on the right. *D*, Hyperextensibility of fifth finger. *E*, Hyperextensibility of thumb. Note in the left hand the hyperextension of the index finger and the abnormal separation of the knuckles. *F*, Hyperextensibility of fingers. *G*, Unusual mobility of hip joints is shown.



D.

E.

F.

G.

CLINICAL MANIFESTATIONS[45,88]

The manifestations of the Ehlers-Danlos syndrome can conveniently be discussed under these headings: cutaneous, skeletal, ocular, and internal.

The Skin[2,11,43,72,77].—Characteristically, the skin in E-D is velvety in appearance and feel. It may also resemble wet chamois in feel. In the infant, it may be impressively white. It is hyperextensible, yet not lax (Fig. 2,*A*).

The term *cutis laxa* is inappropriate in the typical case in young persons. Except as noted below, the skin is truly hyperelastic.*

In addition, the skin is fragile and brittle. Minor trauma may produce gaping, fish-mouth wounds. One of my patients was for a time a professional boxer, a multilating occupation for one with this disorder. Another, 16 years old at the time of study (Fig. 2), had had a total of 148 cutaneous stitches taken during her lifetime. Often stitches hold poorly in the skin,[38,76] and the patients and physicians resort to the use of adhesive tape. In the patient of Brown and Stock,[9] 282 stitches had been taken before count was stopped. Thomas, Cordier, and Algan[89] described slow healing of a skin biopsy site and dehiscence of an ocular incision for removal of an ectopic lens. Packer and Blades[68] observed disruption of an appendectomy scar four times in thirty months. In one of my cases, a surgeon described the tissue at laparotomy as being like wet blotting paper. The tissues at autopsy are likely to be abnormally friable (*v. seq.*).

Very little bleeding occurs from the skin wounds. On the other hand, easy bruisability is the rule and, together with other hemorrhagic phenomena, frequently leads these patients to consult hematologists. The subsequent organization and calcification of the hematomas at times result in one type of pseudotumors.

So-called molluscoid pseudotumors[64,69] develop at pressure points—heels, knees, elbows, etc. These were the basis for the misconceived term of Hallopeau and Mace de Lépinay[15,34]: juvenile pseudodiabetic xanthomatosis. Another type of tumor, small to be sure, seen in these cases is the so-called spherule which is usually pea-sized or smaller, and slips about under the skin an inch or more, without causing the patient any discomfort. These are small fat-containing cysts which may become calcareous.[97] They are most frequently the basis for subcutaneous calcifications which may be demonstrable radiologically,[4,35] another basis being calcified hematomas as noted above. Congenital lipomatosis has been described in association with Ehlers-Danlos syndrome by Tobias.[91] It is entirely possible, however, that the fatty tumors in his case were an integral part of the connective tissue disease. At times actual ossification occurs.[41] The subcutaneous calcifications are characteristically ovoid in shape and 2 to 8 mm. in largest dimensions. They occur principally on the legs and to a lesser extent on the arms. Radiologically they display a diffuse inner calcification with a more dense surrounding shell. They are not laminated like phleboliths. These

*To the physicist *elasticity* means a restoration of initial condition after release of a distorting force. Perfect elasticity means complete recovery after deformation. An inelastic substance is one in which there is no force of restitution. For example, a steel beam is highly elastic in the scientific sense although scarcely so in the conventional popular sense. To the popular mind *elasticity* connotes only in a secondary manner the restitution of original condition. The primary connotation in general usage is stretchability. The term *hyperelasticity* must refer mainly to this latter feature. It is used to indicate a close resemblance to the physical properties of a rubber band.

characteristics, together with the facts that they are not in muscle (as are calcified parasitic cysts) and are too widely distributed to be phleboliths, should permit the radiologist to make the diagnosis of E-D.

Easily recognized changes develop in the skin overlying the knees, shins, and elbows; it becomes shiny, parchment-thin, and hyperpigmented (Fig. 2). Resulting are the so-called "cigarette paper" or "papyraceous" scars. Telangiectases sometimes develop in the region of these atrophic scars. The skin changes may suggest those produced by exposure to x-rays.

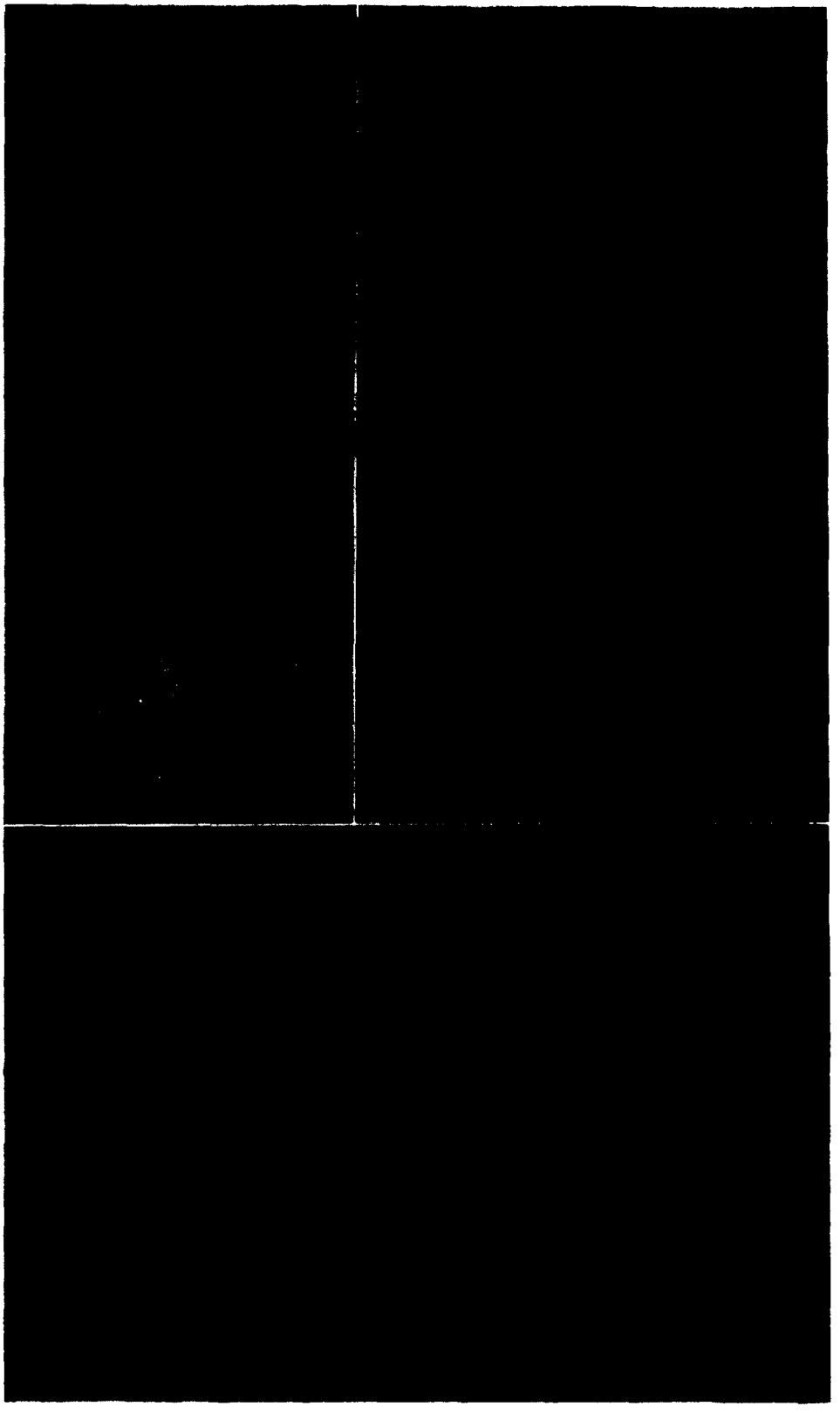
Bleeding may occur from the gums with brushing of the teeth, from tooth sockets after dental extractions, from the pharynx after tonsillectomy, and at the site of operations on the joints.[95] Petechiae in late pregnancy and prolonged post-partum hemorrhage have been described.[78] Contrariwise, in one of my patients it is difficult to get blood for cell counts by finger puncture, and venipunctures are also difficult, seemingly because of very small and collapsed superficial veins. In another of my patients (Fig. 5), a strain of the tendons of the hamstring muscles at the knee resulted in the subcutaneous dissection of blood down to the ankle. E-D must be included in the differential diagnosis of familial hemophilia-like states. All tests of coagulation are usually normal except that the Rumpel-Leede test may be positive.[63]

Blisterlike lesions may develop, suggesting epidermolysis bullosa (see Weber's interpretation of Burrows' case[10]).

The limitation of the cutaneous changes, particularly hyperelasticity, to one side of the body, as recounted by van Meekeren[94] in 1682, is almost completely incredible to the reader but is lent credence by identical reports by DuBois[22] in 1931 and by Murray and Tyars[57] in 1940. Limitation of integumental hyperelasticity to the mucous membranes, specifically those of the mouth and tongue, has been described[21] and many cases have evidences of changes at these sites.[50] It is said that affected women do not get striae gravidarum.[38]

The skin of the hands and the soles of the feet tends to be redundant (unlike most of the skin elsewhere which fits snugly) and with pressure flattens out like a loose glove or moccasin (Figs. 5*A*, *C*, and *D*). A comparable change may develop in later years at the elbows, where the skin may hang lax like a dewlap (see Fig. 5,*B*). In general, late cases tend to show cutis laxa more than cutis hyperelastica, whereas, as emphasized above, cutis laxa is not an accurate designation in the typical case in young persons.

Acrocyanosis and chilblains have been described as a seemingly integral component, by French authors in particular,[26,41,56,60,82] but by others[9,12] as well. There seem to be few American reports of this complaint. In general, chilblains are much less common in this country than in Europe, possibly because of our more universal use of central heating. E-D is at least one basis for acrocyanosis which "runs in a family." It may be the presenting complaint in E-D. For example, Gilbert, Villaret, and Bosviel[29] described a 22-year-old man who had had cyanosis of the hands, feet, and ears from birth and displayed the other characteristic features of E-D. In the patient's family there were several other cases of "cyanosed limbs and ulcerated chilblains" in association with E-D. Burrows[10] provided an excellent photograph of the hand of one of these patients showing both joint hyperextensibility and cyanosis of the fingers.



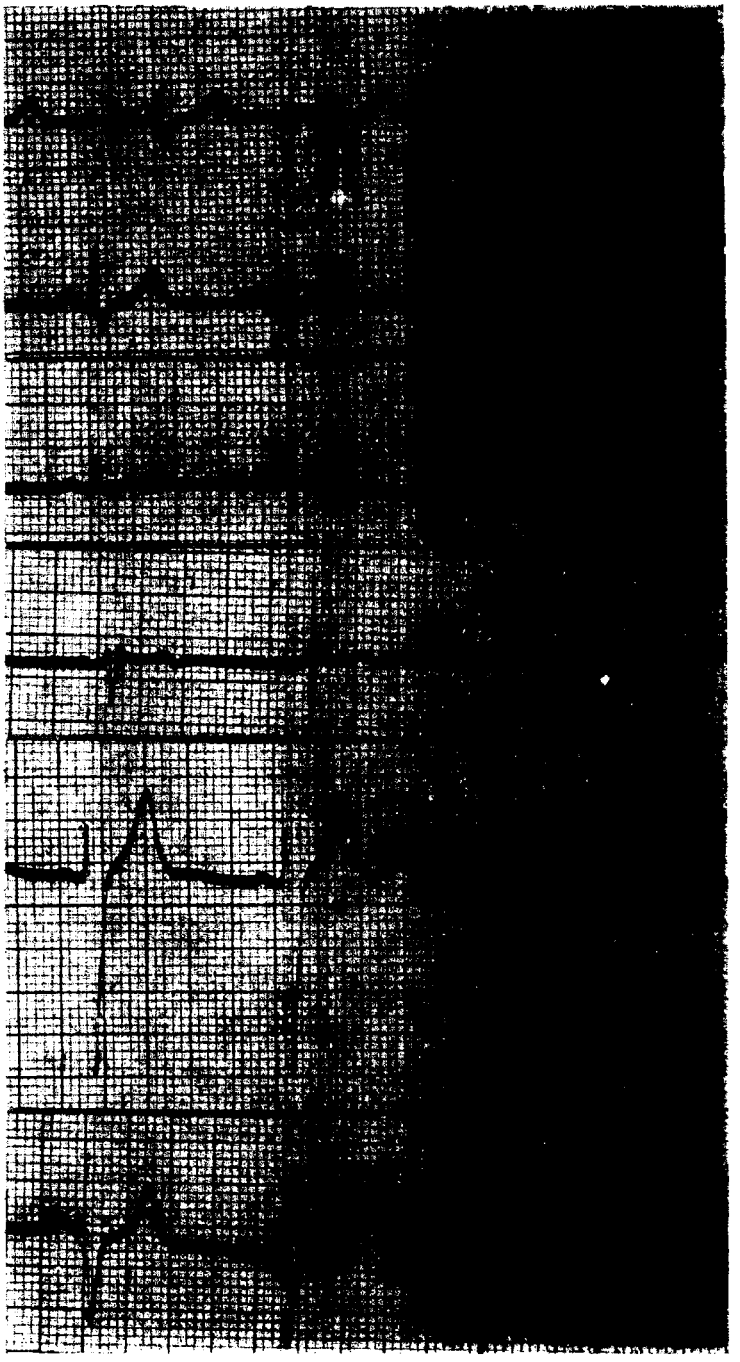
A.

B.

C.

Fig. 3,*A-C.*—(For legend see opposite page.)

Conceivably either the abnormality with hyperelasticity of the supporting tissues about the arterioles or of the connective tissue in the vessel wall itself interferes with blood flow. My observations of difficulties in obtaining blood by fingure puncture or venipuncture (see above) are significant in this connection.



D.

Fig. 3.—Patient aged 35 years. *A*, Note scars of forehead and hyperextensibility of the skin. The patient was a professional boxer for a time. *B*, Note the spherical tumor in the skin of the anterior aspect of the left thigh. Ability to hyperextend the thumb, as in *C*, occurs frequently as an isolated, inherited characteristic.[30,100] *D*, Incomplete right bundle branch block present since at least the age of 19 years and almost certainly all of life. No other cardiovascular or internal medical disorder was demonstrable.

The Musculoskeletal System.—Hyperextensibility of the joints is characteristic (Figs. 2,*D* 2,*E*, 2,*F*, 3,*C*, 4,*A*, 4,*B*). This and the corresponding change in the skin make the victims of advanced forms of this disease the "India rubber men," "human pretzels," and contortionists of side shows. The hyperextensibility tends to become less marked as the patient becomes older. Frequently the patients have joint effusions, especially in the knees, because of traumatization as a result of the joint instability. Flat feet commonly occur from ill-fitting shoes and from what, for these patients, is excessive walking (Fig. 3,*B*). Clubfoot is described.[5] The loose-jointedness, in the knees in particular, may result in a gait and stance suggesting tabes dorsalis[42] (Fig. 2,*C*, 5,*A*). Habitual dislocation of the hip,[15,59,98] patellae,[22,59] shoulder,[65] radii,[42] clavicle,[33] and other joints is a frequent feature. As in Marfan's syndrome, the sternal ends of the clavicle may be very loose.[42] There is likely to be genu recurvatum[98] (see Fig. 2,*C*). The patients are often able to pull their fingers out longitudinally for an appreciable distance and allow them to snap back into place on release. Kyphoscoliosis is likely to develop.[16,42,59,75,87,99] Spina bifida occulta is described.[44] Arachnodactyly[41] and deformity of the pinnae also occur. Dental deformities are frequent[26,42,58] and Gothic palate may be present.[40] Muscular hypotonicity and underdevelopment seem to exist in these patients. In one of my cases, a 4-year-old child, amyotonia congenita of Oppenheim was the initial diagnosis. Smith[82] describes a similar experience. Hernias occur frequently.[97] In some, repair of an umbilical hernia at a young age is necessary.

Ectopic bone formation with formation of osseous bridges between the acetabula and the femoral trochanters have been described by Katz and Steiner.[41] The pathogenesis may have involved hemorrhage from increased joint mobility.

The Eye.—Changes have been described in the ocular adnexa, the cornea, the sclera, the suspensory mechanism of the lens, and the fundus.

The skin about the eyes often lies in redundant folds and can be pulled out to a considerable distance like the skin elsewhere. Epicanthal folds are frequent. Méténier[54] has lent his name to a frequent phenomenon, namely, unusual ease in everting the upper lid.

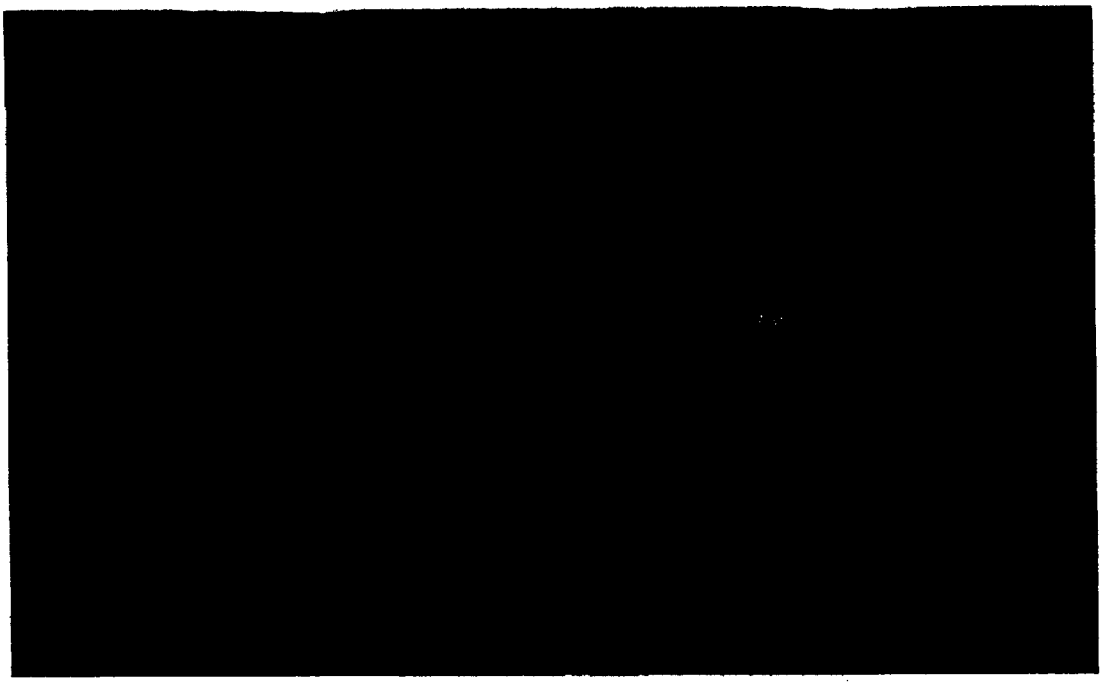
Blue sclerotics have been described commonly.[6,24,90] Microcornea with associated glaucoma was described in one patient[24] in whom the small size of the cornea was thought to be responsible, at least indirectly, for an impediment to occular drainage. Keratoconus is also described.[90]

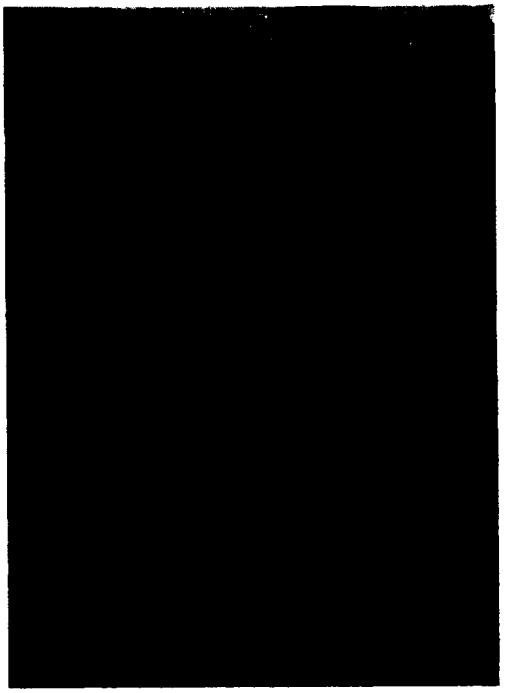
Ectopia lentis occurred in at least one twice-reported patient.[89,90]

In one patient, the authors[5] described and illustrated changes in the fundus consisting of retinitis proliferans, pigment spots which were interpreted as residua of microhemorrhages, and detachment of the retina of secondary type (no retinal tear was detected).

Internal Ramifications.—The internal manifestations of E-D have not been investigated to any significant extent. Those manifestations which have been identified include (1) diaphragmatic hernia, (2) ectasia of portions of the alimentary and respiratory tracts, (3) spontaneous rupture of the lung, (4) dissecting aneurysm of the aorta, and (5) certain congenital malformations of more conventional type.

A.





B.

Fig. 4.—C. G. (287731), 47 years old. Long history of "congenital dislocation of right hip," treated with a spica at the age of 2 years and with several operations in his twenties. Bilateral inguinal hernias repaired. Hiatus hernia is apparently responsible for epigastric and substernal pressure, which occurs especially in the recumbent position and is relieved by belching. Two operations on knee for presumed trauma of automobile accident. At the age of 27 years, "relaxation of right radiocarpal joint" necessitated application of a cast. Hyperelasticity of the skin, although present, was a subsidiary feature in this patient.

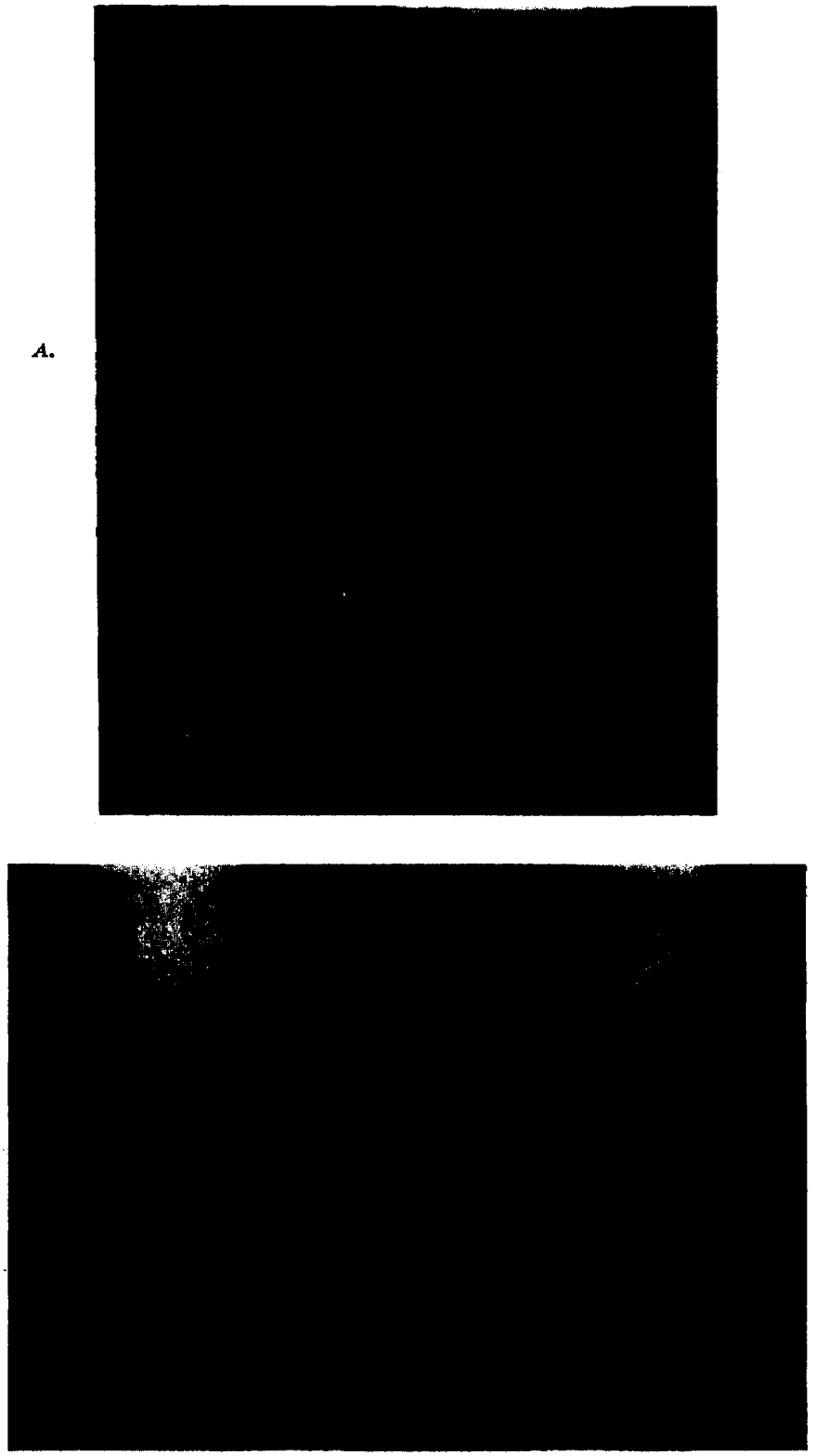
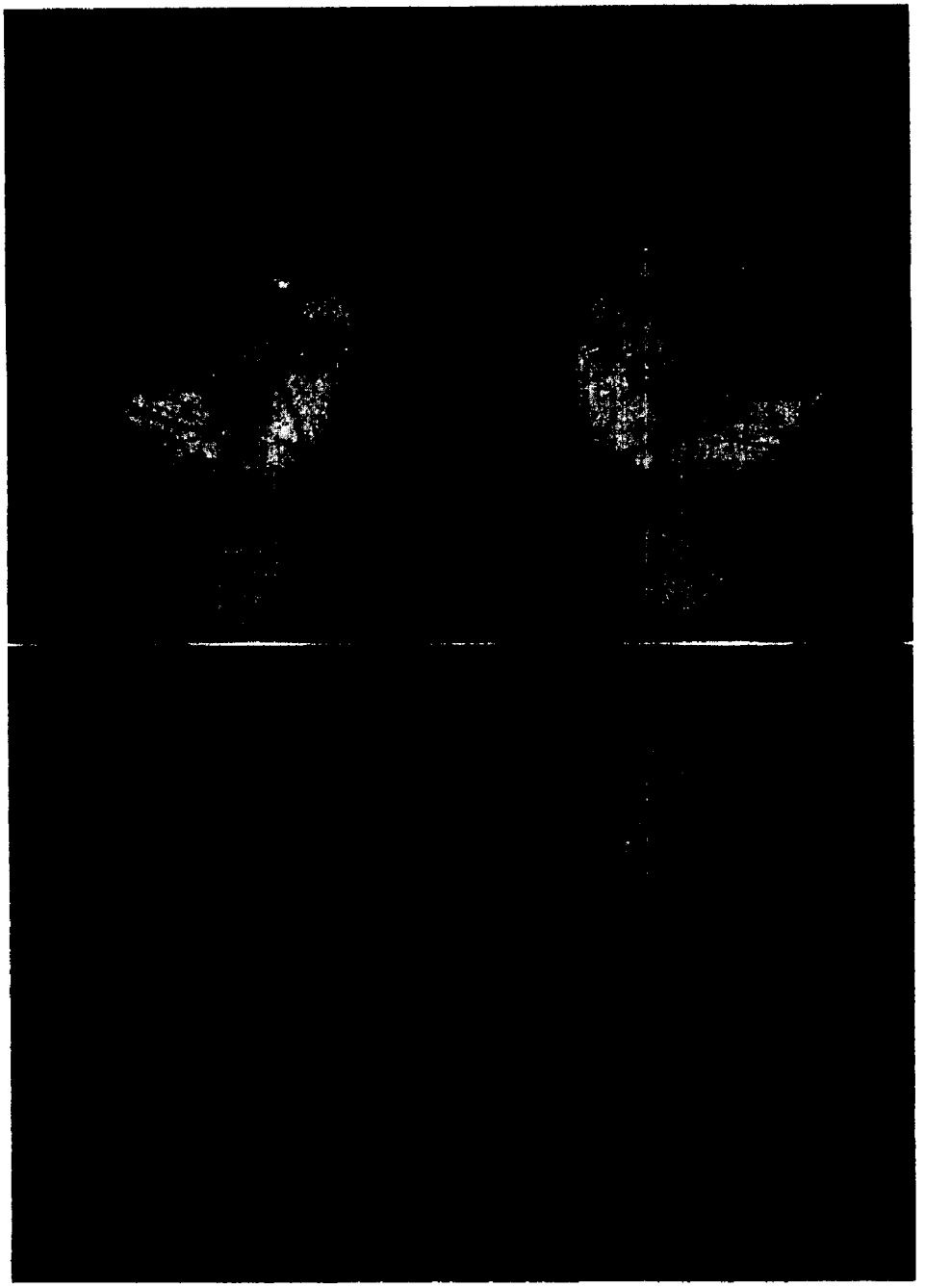


Fig. 5.—K. W. (667280), 48-year-old man. *A*, Note deformity of feet, molluscoid tumors around heels (seen less distinctly in Fig. 2,*B*). The soles appeared to be loose-fitting and like moccasins. *B*, Dewlaps of both elbows.

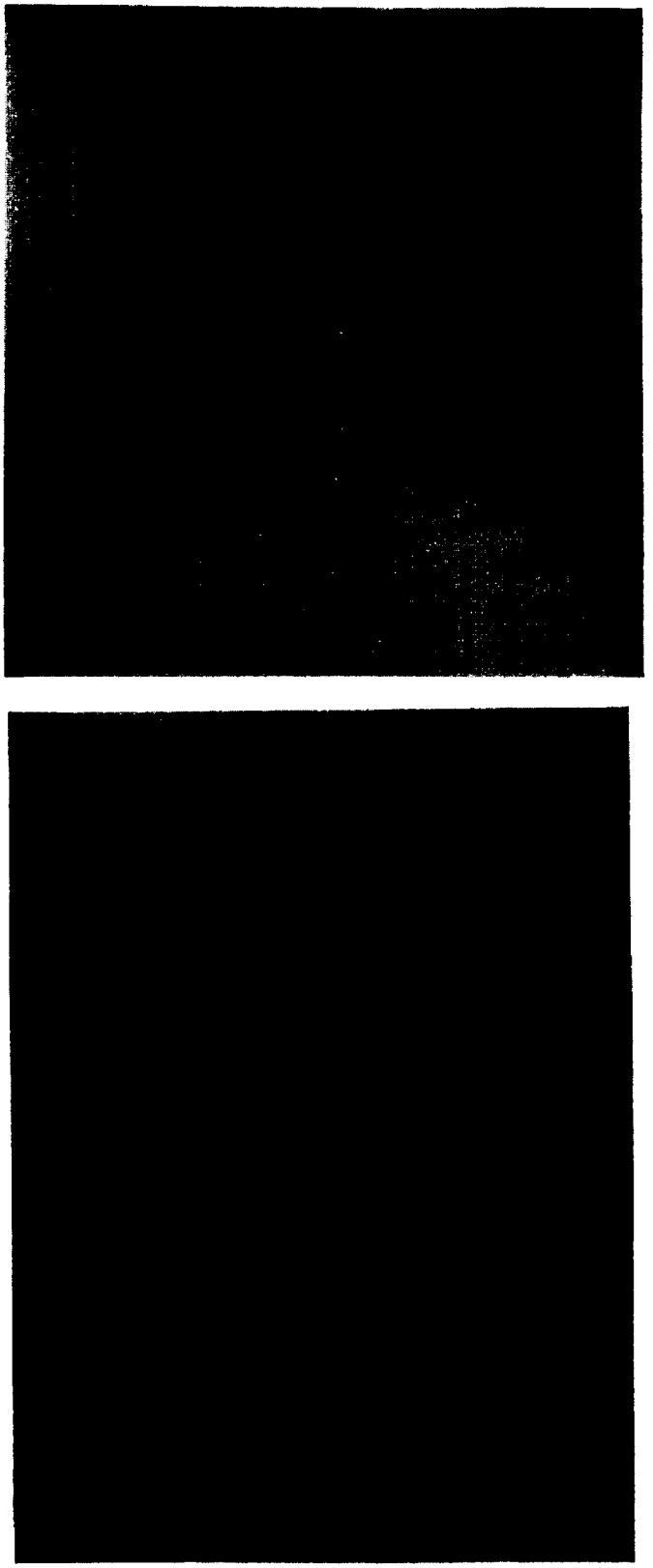
One of my patients has eventration of the left leaf of the diaphragm (see Fig. 5,*E*). Differentiation from a large posterior diaphragmatic hernia is uncertain. We have observed hiatus hernia in a second patient of whom other illustrations are shown in Fig. 4. Brombart, Coupatez, and Laurent[7] described a patient in whom hiatus hernia, diverticulum of the stomach, duodenal diver-



C.

D.

Fig. 5, *C* and *D*.—Comparable lax and furrowed skin of the hands.



E.

F.

Fig. 5, *E* and *F*.—*E*, Posterior eventration of diaphragm. *F*, Anomaly of ureteropelvic function, bilaterally. Nonfunctioning kidney on left.

ticulum, and colonic diverticulosis occurred in association with E-D. Megaesophagus, megatrachea, and megacolon were described in another case.[66] Bladder diverticulum is described.[86]

In one reported patient,[63] repeated episodes of mediastinal and subcutaneous emphysema occurred, and we have observed spontaneous pneumothorax in one patient. It is to be noted that in the first case of dissecting aneurysm described below, the lungs revealed subpleural blebs, and subcutaneous emphysema was present.

Fatal dissecting aneurysm of the aorta has been observed by me in two patients in whom the diagnosis of E-D is distinctly possible. Interestingly, the histologic changes in the aorta in at least one of these were those of Erdheim's cystic medial necrosis and indistinguishable from those discovered in some cases of the Marfan syndrome. Abstracts of these two cases follow.

CASE 1.—H. L. R.,* a 15-year-old Negro student, with a history of always having been sickly, was thrown forcibly to the ground by a schoolmate. He complained immediately of pain in the chest extending down the right arm and soon developed signs and symptoms of circulatory collapse. He was taken to the neighboring office of a physician, where he died within ten minutes.

Autopsy revealed an adequately developed and nourished Negro male weighing 140 pounds and measuring 5 feet 6 inches in height. The skin showed many scars; some resembled burn scars. One on the right thigh was covered with thin epidermis and measured 15 by 3.8 cm. wide. An ulcer with hemorrhagic base, 25 cm. in diameter, was located on the medial aspect of the left ankle. There was considerable subcutaneous emphysema below the right rib margin.

During the dissection the connective tissues were found to be very friable. They tore easily and even the skeletal muscles pulled apart with incredible ease. (The autopsy was performed only a few hours after death. The tissue were not autolyzed histologically. Dr. Thoma, the prosector, had never encountered such fragility of tissues and considered it highly significant.) Fourteen hundred cubic centimeters of blood was found in the right hemithorax. The mediastinal structures were infiltrated with blood which also had dissected along the fascial planes of the neck. The lung showed multiple large emphysematous subpleural bullae and were easily torn. The heart weighed 300 grams. The gastrointestinal tract tore easily.

Histologic studies, including stains by the periodic-acid-Schiff method and elastic tissue stains, were unrevealing of definite abnormality.

Further investigations of the boy's previous health and of his family revealed that he had always been sickly, did not play as actively as his contemporaries, and often complained of severe headache. He "cut" his skin easily and healed poorly. At the age of 11 he had sprained his ankle; x-rays of the injured part were not considered abnormal on review.

The father of the patient died at the age of 21 or 22 years of asthma. The mother died at the age of 22 years after a twenty-four-hour illness, beginning with abdominal pain, nausea and vomiting, and characterized by progressive circulatory failure. Autopsy was not performed but the diagnosis given on the death certificate was "internal hemorrhage of unknown cause." There were no siblings of the propositus.

CASE 2.—J. M. M.,† a 24-year-old white man, was well until 6 A.M. on the morning of Dec. 31, 1946, when he awoke with a vague discomfort in the abdomen. In the course of two hours this developed into pain in the right flank and lower quadrant of the abdomen. By the time he was admitted to the hospital, a few hours after onset, he was in profound shock. The administration of fluids intravenously raised the blood pressure from an indeterminably low level to

*For calling this case to my attention I am indebted to Robert Osborne, fourth year student, Medical College of Virginia. For much information bearing on the case I am indebted to Dr. George W. Thoma, formerly Assistant Chief Medical Examiner, Commonwealth of Virginia.

†I am indebted to Dr. John F. Brownsberger of Takoma Park, Maryland, for much information on this patient.

90/60 mm. Hg. The white count was 25,000 and 28,000 per cubic millimeter on two determinations. The hemoglobin concentration fell from 82 to 69 per cent of normal during the afternoon. By 3 P.M. the patient was complaining of pain in the region of the right shoulder. Abdominal exploration was undertaken at 5 P.M. The abdomen contained blood-stained fluid. A large retroperitoneal hematoma involved the right kidney. There was dissection into the mesentery which was torn in several places. The surgeon compared the tissues to wet blotting paper. Bleeding and clotting times determined postoperatively were 1 and 4 minutes, respectively. The patient died at 4:15 A.M. on Jan. 1, 1947.

Subsequent investigations revealed that the patient had always bled and bruised easily. He also had sustained a number of fractures. The possibility of minor trauma during the previous evening could not be excluded.

Autopsy revealed a body measuring only 62 inches in length. Despite this, arachnodactyly was thought to be very impressive. The prosector may have been unduly impressed because of the recognized association of arachnodactyly and dissecting aneurysm. During the opening of the chest at autopsy the ribs were thought to fracture with abnormal ease. The abdomen contained 500 c.c. of bloody fluid. The aorta and the renal and iliac arteries were described as hypoplastic. A dissection of the right renal artery with infarction of that kidney was discovered. Histologically the media of the aorta was thin with numerous areas of "myxomatous degeneration" and basophilically staining material. There was some fragmentation of the elastic fibers which seemed to be normally abundant but morphologically abnormal. The renal artery showed marked fragmentation of elastic fibers.

Although the second patient was included as an instance of arachnodactyly in reports[31,32] of a series of cases of dissecting aneurysm, the short stature, the easy bruisability, and the friability of the tissues at operation and at autopsy suggest E-D.

One reported patient had interatrial septal defect[26]; another had tetralogy of Fallot.[96] A loud systolic murmur in the pulmonary area, audible also in the left interscapular area of the back, was described in one patient.[52] One of my patients has demonstrated for many years, probably all his life, the electrocardiographic pattern of incomplete right bundle branch block without subjective or other objective cardiovascular manifestations (Fig. 3,*D*).

Another of my patients has a bilateral congenital anomaly of the ureteropelvic junction (Fig. 5,*F*). In the case of Marfan's syndrome it was pointed out that there are a number of manifestations which are congenital malformations in the conventional sense and which occur often enough to be considered bona fide components of the syndrome. It was proposed that these are secondary manifestations, that the hereditary disorder of connective tissue creates an ontogenetic setting in which certain predictable congenital anomalies occur with increased frequency. In E-D, ureteropelvic anomaly, tetralogy of Fallot, and interatrial defect may fall into this category of secondary manifestations. However, since to my knowledge, each has been described in only one patient, it is equally reasonable to suspect that these manifestations may have occurred by accident.

As a rule, mental retardation is not a feature of this syndrome. However, occasionally patients show it, probably as a coincidentally associated finding.[48,50] Severe essential hypertension occurred in one patient as a probable incidental finding.[41]

PATHOLOGY

In none of the five disorders of connective tissue discussed in this series is the microscopic anatomy in such a disputed state as in E-D.[45]

Increase in elastic tissue of the corium has been described by many writers.[1,6,38,54,55,70,71,76,83,89,91] Some of these described morphologic abnormalties of the elastic fibers, as did Smith[82] and Pittinos,[68] who, however, did not consider the elastic fibers to be more numerous than normal. Williams[102] and Pautrier[64] found the elastic fibers *normal*, and Brown and Stock[9] believed them to be *decreased.*

Diminution and morphologic abnormalities of collagen fibers have been described.[62,82,91] Katz and Steiner[41] report histochemical studies which they interpret as indicating increase of mucopolysaccharide of corium.

Jansen[36] points out, with excellent illustrations, that "in normal skin, a system of robust, well directed, crossing and tightly interlacing collagen fibre bundles is present. The whorled disorderly structure in hyperelastic (E-D) skin is remarkable; the collagen bundles seem to have been insufficiently united." By electron microscopy collagen and elastin were morphologically normal. This corrborates the finding of Tunbridge and his collaborators,[92] but Jansen was unable to agree that there was an absolute increase in the number of elastic fibers.

Collections of giant cells are sometimes found.[75] The subcutaneous nodules or spherules are apparently fat-containing cysts.[97] They frequently become calcified. It seems likely that they are related to minor traumata and to the general fragility of the connective tissue in which the fat deposits normally exist.

How much of the bleeding is due to a defect in the supporting tissues and how much due to weakness of the vessel walls themselves is not clarified by histologic studies. Abnormal, dilated, weak-appearing vessels have been described by Tobias[91] and others.[50]

Unfortunately, studies of tissues other than skin have not been reported with the exception of an autopsy case described by Leinhart[50] and, of course, the two cases of dissecting aneurysm described above. In Leinhart's patient, a 22-year-old woman who died of pulmonary tuberculosis, no internal abnormality referable to the connective tissue defect was discovered.

THE BASIC DEFECT

Superficial consideration of the clinical manifestations of E-D might suggest an abnormality of elastic tissue as the fundamental defect, probably a superabundance of elastic fibers in the skin and joint capsules. However, the histologic studies by no means afford unequivocal substantiation of this theory. Brown and Stock[9] suggested, and others (notably and most recently Jansen[36]) maintain,[28] that the defect may reside in the collagen fibers which, because of lack of normal tensile strength, permit the skin, joint capsules, ligaments, and so forth, to be stretched beyond the normal limits. The elastic fibers may function in connection with the process of restoration to normal configuration of these tissues. According to the "collagen theory," the histologic changes, both

quantitative and qualitative, are interpretable as secondary effects of the abnormality of collagen. I am inclined to favor the view that the Ehlers-Danlos syndrome is another heritable disorder of collagen, biochemically, morphologically and clinically distinct from the others which are under discussion in this series.

The comparative inextensibility of normal collagen may depend upon some specific molecular or intermolecular structure which is altered in E-D with resulting increase in extensibility. This is assumed to be the case in the theory of Brown and Stock and has been explicitly stated by Froelich[27] and others. Jansen[36] has recently advanced a related theory incriminating collagen but placing the defect at a higher level of organization of collagen, i.e., that E-D is a disorder of the organization of collagen fibrils into bundles and of the bundles into a strong network. He refers to the disease as one of a "defective wickerwork" of collagen. The evidence he assembles (see above, under Pathology) and the clinical aspects of the disease outlined here make Jansen's version of the "collagen theory" highly probable.

It is possible that in some patients and at some subcutaneous and articular locations production of an excessive member of elastic fibers is stimulated by the repeated and excessive stretching. In tissue culture, Maximow[63] and Bloom[3] thought the tugging of contractile myocardial cells was a factor in the formation of elastic fibers.

The changes in the skin of the feet and hands and at the elbows of older patients fit in well with the view that the primary defect resides in the collagen fibers: the normal elastic tissue may, with the passage of time, "wear out" from excessive stress imposed upon it, and the cutis laxa (as opposed to cutis hyperelastica) of late cases become evident.

INCIDENCE AND INHERITANCE

Thus far, this syndrome has been described principally in Europeans and persons of European extraction. There is one report from India[12] of the disease in a 12-year-old Hindu girl. I know of no report of the condition in Negroes and have encountered the disease in only one possible instance, the first case of dissecting aneurysm above.

Schaper[79] stated in 1952 that only 93 cases of this syndrome had been reported. Although the number is now probably well in excess of 100, it is possible that fewer of these cases have been reported than of any of the other syndromes discussed in this series. This is in part the result of greater difficulties of recognizing the syndrome, since cutaneous and articular hyperelasticity is a graded trait. I hazard to say, however, that in actuality this is one of the most frequent of the heritable disorders of connective tissue. My photographer, in the course of the study of other patients with E-D, recalled that his brother-in-law could do contortionist tricks with his hands. On investigation this individual was found to have had congenital dislocation of the right hip, bilateral inguinal hernias, diaphragmatic hernia, trouble with one knee and the right wrist (Fig. 4). Although these had all been considered unrelated, the diagnosis of the Ehlers-Danlos syndrome is quite certain and all these manifestations are clearly part of the syndrome. This patient illustrates how easy it is to overlook the generalized disorder.

The incidence of this syndrome, at least the frequency with which the diagnosis is made, relative to that of other heritable disorders of connective tissue, is indicated by the fact that available to me for study have been only eight kinships in which at least one bona fide instance of E-D has occurred, whereas over fifty Marfan kinships, forty to fifty osteogenesis imperfecta kinships, sixteen pseudoxanthoma elasticum kinships, and fifteen kinships with the Hurler syndrome have been collected by tapping all possible sources of index cases.

In at least three of the eight kinships I have studied, more than one affected person was identified: father-daughter; mother-son; mother-mother's cousin-daughter. Since mild manifestations tend to be overlooked by laymen and since only the propositus was examined in several instances, the above evidence can be taken only as a rough indication of the pedigree pattern which may be observed.

Johnson and Falls[38] reviewed sixteen families reported in the literature as having more than one affected member.[33,44] In these families, a total of eighty affected individuals had been identified, of whom exactly half were male. Brown[8] found nineteen affected members in a family numbering forty-seven individuals. Johnson and Falls[38] studied the pattern of inheritance in detail and concluded that the disorder is inherited as a dominant. Two sisters with an unusually severe form of the disease were children of cousins, each with a mild form of the disease; this suggested to the authors that the trait might have occurred in homozygous state in these girls. Consanguinity was thought to be a factor in the cases observed by Ronchese[76] and by Weber and Aitken.[97]

Coe and Silver[13] presented illustrations of members of three generations displaying the E-D syndrome, and Stuart[84] traced it through four generations. Here there was again clear evidence of dominant inheritance. The disease has been described in one of twins who were probably fraternal.[20] A number of pedigrees[95] have been reported since 1949 when Johnson and Falls collected 16 kinships with more than one case.

Penetrance in this disease is probably considerably lower than in Marfan's disease, for example. This, however, is merely the result of the greater difficulty of recognizing mild and graded abnormality of the joints and skin as opposed to less equivocal manifestations, e.g., ectopia lentis, in Marfan's syndrome.

MISCELLANEOUS CONSIDERATIONS

"Simple" hypermobility of joints, known also as congenital laxity of ligaments, may occur as an isolated finding[42,73,85] with a genetic background distinct from that in E-D. For example, in Key's family[42] a sex-linked inheritance was suggested; the disorder occurred only in males. Loose-jointedness occurs also in the Marfan syndrome and with osteogenesis imperfecta, whereas reduced joint mobility is characteristic of the Hurler syndrome. In the differential diagnosis of loose-jointedness, especially in children, cerebrocortical degeneration or malformation, mongolism, cretinism, rickets, and nonspecific cachexia must be kept in mind.

Blue sclerae are not uncommon in E-D,[6,24] and presence of this feature cannot be taken as evidence of associated osteogenesis imperfecta. The description[50,74] of associated dolichostenomelia (long, thin extremities as in the

Marfan syndrome) cannot be taken as evidence that E-D and the Marfan syndrome coincided in those patients, since no ectopia lentis was detected and no unequivocal cases of the Marfan disease in other members of the family were described.

At least three seemingly bona fide instances of coincident E-D and pseudoxanthoma elasticum have been described.[14,59,65] In Cottini's patient[14] there were angioid streaks and lesions of the skin of the neck characteristic of pseudoxanthoma elasticum (see Section VI of this series) and, in addition, cigarette paper scars of the elbows and knees and hyperextensible skin and joints characteristic of E-D. The pseudoxanthoma elasticum, which appears to be a recessive trait, was not transmitted to a daughter who suffered from acrocyanosis or a son who had hyperextensible skin and joints, hernia, and varices of the leg veins. The 22-year-old woman described by Pelbois and Rollier[65] consulted them because of the cosmetically undesirable lesions of pseudoxanthoma elasticum involving the skin of the neck and other areas of flexure. As well as angioid streaks of the fundus (characteristic of pseudoxanthoma), the patient had multiple cicatrices indicative of cutaneous fragility, striking cutaneous hyperelasticity, and articular hypermobility. The parents were first cousins, a fact significant in the appearance of the recessive trait, pseudoxanthoma. The parents were themselves unaffected by pseudoxanthoma although a maternal aunt of the patient was affected. As for E-D, the patient's mother displayed features of this syndrome and had probably transmitted it as a dominant trait to her daughter. These are then examples of accidental coincidence of the two syndromes, one behaving as a dominant and one as a recessive trait.

In one patient, 61-years-old,[58] E-D coexisted with muscular atrophy of the Aran-Duchenne type (amyotrophic lateral sclerosis). I find it impossible to agree with the authors[58] that an etiologic connection between the two conditions existed. In one of my cases, Oppenheim's disease (amyotonia congenita) was the original diagnosis when the patient was first seen at the age of 4 years. Abnormality of creatine meatoblism was reported in one patient[68] and in another[66] there was coincident parathyroid tumor with osteitis fibrosa cystica. After correction of the hyperparathyroidism surgically, it appeared that the joint laxity, particularly the scoliosis, and the fragility of the skin decreased.

Interesting physiologic studies of skin elasticity and tensile strength have been done in recent years.[18,19,38,46,60,75,99] Rollhäuser[75] found least tensible strength in the skin of infants under 3 months (about 0.25 kg. per square millimeter); more in adults (about 1.6 kg. per square millimeter) and yet more in aged individuals (over 2.0 kg. per square millimeter). With aging, furthermore, skin became progressively less extensible. These observations may explain the tendency for the cutaneous fragility and extensibility in E-D to become less striking as the affected individual ages. Rollhäuser[75] studied the skin tensile strength of a 35-year-old man with E-D and found it to be very low (0.34 kg. per square millimeter). It is of interest that this worker found parallel changes in the tensile strength and extensibility of tendons, suggesting that the properties measured in the skin may be constitutional and generalized. Wenzel[99] found lesser tensile strength in female skin and made important observations indicating

reduction in the strength of the skin in normal pregnancy and in Cushing's syndrome. In connection with the latter condition, it is noteworthy that the fragility of the skin and easy bruisability are rather similar in E-D and in Cushing's syndrome.[47] However, in all likelihood, the similarity is only superficial.

SUMMARY

On the basis of eight kinships containing at least one previously unreported case of the Ehlers-Danlos syndrome, and on the basis of the cases reported in the literature, the cardinal manifestations of the syndrome can be said to be hyperelasticity and abnormal fragility of the skin and hyperextensibility of joints. Other cutaneous and skeletal manifestations which are an integral part of the syndrome are discussed as well as ocular and internal manifestations.

It is suggested that dissecting aneurysm of the aorta may be a complication of this connective tissue disorder as well as of the Marfan syndrome. Diaphragmatic and other types of hernia occur fairly often and conventional types of congenital heart disease and congenital anomalies of the kidney have been observed. Rupture of the lung with mediastinal emphysema and/or pneumothorax appears to occur with increased incidence.

The best information appears to indicate that the basic defect is one of the organization of collagen bundles into an intermeshing network.

The disorder is probably inherited as a Mendelian dominant.

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